UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,637	11/25/1997	ELAZAR RABBANI	Enz-53(D5)	4643

28171 7590 11/02/2011

ENZO BIOCHEM, INC.
527 MADISON AVENUE (9TH FLOOR)
NEW YORK, NY 10022

EXAMINER	
MCDONALD, JENNIFER SUE PITRAK	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
11/02/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,637	RABBANI ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK MCDONALD	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

5a) Of the above claim(s) *318-323* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *265,268,270,272,284,290,296,299,303,304,308,312,313,325 and 326* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 265,268,270,272,284,290,296,299,303,304,308,312,313,318-323,325 and 326.

DETAILED ACTION

Remarks

Applicant's remarks filed 9/9/11 have been entered and considered. Claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 318-323, 325, and 326 are pending. Claims 318-323 are withdrawn. Claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325, and 326 are under examination.

Response to Arguments

Applicant's arguments with respect to claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325, and 326 have been considered but are moot in view of the new ground(s) of rejection.

Withdrawn Rejections

The rejection of claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325 and 326 under 35 U.S.C. 103(a) as being unpatentable over Izant (Chimeric Antisense RNAs, in Gene Regulation: Biology of Antisense RNA and DNA, pages 183- 195 (Erickson, R.P and Izant, J.G., eds.; Raven Press, Ltd: New York) (1992), Frankel et al (USPN 5,989,814), and Zieve et al (Critical Rev. in Biochem. & Molec. Biol., Vol. 25, No. 1, pages 1-46, 1990), the combination in view of Meador et al., Dahlberg et al (The Genes & Transcription of the Major Small Nuclear RNAs, in Structure and Function of Major & Minor Small Nuclear Ribonucleoprotein Particles, pages 38-70, Max L. Birnstiel, Ed., Springer-Verlag: New York,

1988), Calabretta et al. (USPN 5,734,039) and Binkley et al (Nucleic Acids Research, 1995, Vol. 23, No. 16, pages 3198-3205), the combination further in view of Craig et al (WO 95/08635) and Alul et al (USPN 5,532,130) is **withdrawn.**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 268, 270, 296, 299, 303, 304, 308, 312, 313, 325, and 326 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 265 is directed to

> An isolated nucleic acid construct which when present in a cell acts as a template for the synthesis of a nucleic acid comprising (i) a nuclear localization sequence comprising a portion of U1, U2 or U4 snRNA, said portion of U1, U2 or U4 snRNA comprising sequences for (a) at least two stem loops present at the 3' end of native UI, U2 or U4 snRNA, and (b) a reimportation signal and (ii) an antisense nucleic acid sequence, wherein said antisense nucleic acid sequence replaces stem-loop sequences removed from said U1, U2 or U4 snRNA that are not in said two stem loops present at the 3' end of said snRNA.

The claim requires the production of RNA from the claimed template isolated nucleic acid construct. Claim 268 is directed to

> The nucleic acid construct of claim 265, wherein said antisense nucleic acid (ii) is selected from the group consisting of DNA, RNA, a DNA- RNA hybrid, a DNA-RNA chimera, and a combination of the foregoing.

The "antisense nucleic acid" of claim 265 cannot be DNA, DNA-RNA hybrid, or a DNA-RNA chimera. A nucleic acid construct(ion) when present in a cell is either a template for DNA (via replication or reverse transcription) or RNA (via transcription). Because claim 265 specifies the production of RNA from the template construct, claim 265 is limited to a construct that acts as a

template for transcription (RNA synthesis). Therefore, claim 268 is indefinite.

Claim 270 recites the limitation "said nuclear localized sequence". There is insufficient antecedent basis for this limitation in the claim.

Claim 295 is indefinite because it requires that the nucleic acid construct(ion) of claim 265 comprises U1 or U2 snRNA or both. The nucleic acid construct of claim 265 must be DNA, because it is a template for transcription of RNA.

Claims 303 and 304 are indefinite because they are directed to the nucleic acid construct(ion) of claim 299, wherein the nucleic acid in the construct is DNA, RNA, nucleic acid analogs, or a combination thereof. The construct of claim 299 must be DNA because the construct contains a promoter that produces nucleic acid from that promoter. Promoters direct transcription, which is the production of RNA.

Claim 312 is indefinite because it is directed to the nucleic acid construct of claim 299, wherein the construct produces antisense DNA. However, the construct of claim 299 must produce RNA because the construct contains a promoter that produces nucleic acid from that promoter. Promoters direct RNA transcription from DNA templates.

Claim 312 recites the limitation "said specific nucleic acid produced". There is insufficient antecedent basis for this limitation in the claim. Claim 299 is directed to at least three "specific nucleic acid(s)".

Claims 299, 303, 304, 308, 312, 313, 325, and 326 are indefinite. Claims 299, 303, 304, 308, 312, 313, and 325 are directed to constructs that produce specific nucleic acids, each of which is "either complementary with a specific portion of one or more viral RNAs in a cell or binds to a specific viral protein". Claim 326 is directed to a construct that produces specific

nucleic acids, each of which is "either complementary with a specific portion of one or more HIV RNAs in a cell or binds to a specific HIV protein". The claims are further limited to, "wherein each specific nucleic acid so produced binds to different target nucleic acid sequences." This final limitation (present in claims 299, 325, and 326) renders the claims indefinite because it further limits the claims with regard to the production of nucleic acids that are "complementary with a specific portion of one or more viral RNAs" but the phrase does not further limit the claims with regard to the production of a nucleic acid that "binds to a specific (viral/HIV) protein". Therefore, the presence of the phrase "wherein each specific nucleic acid so produced binds to different target nucleic acid sequences" renders the claims indefinite because it is directed to only a portion of the claimed subject matter, such that one of skill in the art cannot determine whether the claimed subject matter is complementary nucleic acids or protein-binding nucleic acids.

Claim Rejections - 35 USC §§ 102 and 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for

patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Crespi, et al.

Claims 299, 303, 304, 308, 312, 313, and 326 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over **Crespi, et al.** (U.S. Patent 5,429,948).

The claims are directed to an isolated multi-cassette nucleic acid construct comprising at least three copies of a promoter, which produces at least one specific nucleic acid from each promoter, wherein each specific nucleic acid is nonhomologous with each other and is either complementary to a specific portion of one or more viral RNAs or binds to a specific viral protein.

Crespi teaches plasmid constructions, which are engineered or modified DNAs, comprising three copies of the HSV promoter and polyadenylation signal, wherein each copy of the promoter drives transcription of a distinct sequence (Figures 4 and 5; column 15, lines 33-44). For example, Figure 4 shows the HSV promoter driving transcription of three distinct cDNAs, one of which is cytochrome p450 IA2. Cytochrome p450 IA2 (CYP1A2) contains complementarity to human immunodeficiency virus as shown here:

```
CYP1A2 (GI|73915099)     5'-CAGCTTCCTCAT-3'
                            ||||||||||||
HIV (GI|9629357)         3'-GTCGAAGGAGTA-5'
```

Thus, the other cDNA sequences of Crespi may have similar complementarity to HIV or other viruses. Therefore, Crespi fairly teaches the limitations of the instant claims, wherein the

cDNAs in the plasmids of Crespi inherently possess complementarity such as is shown above for the CYP1A2 cDNA sequence. See MPEP 2112 (III-V). Crespi also teaches means of introducing the plasmids of their invention into cells (column 18, lines 30-38). Therefore, the claims are anticipated by or obvious over Crespi.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Greatbatch, et al. and Rossi, et al.

Claims 299, 303, 304, 308, 312, 313, 325, and 326 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Greatbatch, et al**. (US Patent 5,324,643) and **Rossi, et al**. (US Patent 5,144,019).

The claims are directed to an isolated multi-cassette nucleic acid construct comprising more than one (claim 325) or at least three copies (claims 299,326) of a promoter, which produces at least one specific nucleic acid from each promoter, wherein each specific nucleic acid is nonhomologous with each other and is either complementary to a specific portion of one or more viral RNAs or binds to a specific viral protein. Claim 325 specifies that the promoter is an snRNA promoter or a bacteriophage promoter.

Greatbatch teaches synthetic or modified plasmid vectors comprising multiple HIV antisense sequences, each transcribed by a copy of a Pol III promoter and introducing such vectors into host cells (abstract; figures 15 and 22-24; claims 1-33). Greatbatch does not teach that the Pol III promoter is an snRNA promoter.

Rossi, et al. teach plasmids encoding T7-promoter-driven expression of HIV-1-targeted ribozymes.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a plasmid encoding multiple HIV antisense RNAs, as taught by Greatbatch. It further would have been obvious to make a plasmid encoding HIV antisense or ribozymes, because Greatbatch and Rossi teach HIV antisense and ribozymes as means by which to combat HIV infection. It further would have been obvious to use an snRNA promoter or T7 promoter in such plasmids because Greatbatch teaches the use of Pol III promoters, which transcribes U6 snRNA and tRNA, and Rossi teaches the use of T7 promoters. It would have been obvious to make a plasmid having three or more HIV antisense or ribozyme sequences, because both Greatbatch and Rossi teach targeting more than one HIV gene, Greatbatch teaches the antisense vectors for the purpose of inhibiting multiple HIV genes at one time, and Greatbatch teaches vectors comprising three distinct HIV antisense sequences. One of skill in the art would recognize that the same Pol III promoter or T7 promoter could be used to drive each of the antisense or ribozyme sequences because Greatbatch teaches the use of a Pol III promoter to drive transcription of each of the HIV antisense sequences and Greatbatch uses the same promoter more than once in the same plasmid. Therefore, the instant claims would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Izant, et al. and Zieve, et al.

Claims 265, 268, 270, 272, 284, 290 and 296 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Izant, et al**. (1992, "Chimeric Antisense RNAs" in Gene Regulation: Biology of Antisense RNA and DNA, pp.183-195) (of record) and **Zieve, et al**. (1990, Critical Rev. Biochem. & Molec. Biol., v.25, no. 1: 1-46) (of record).

The claims are directed to an isolated nucleic acid construct that is a template for a nucleic acid comprising a nuclear localization sequence comprising a portion of U1 RNA comprising C and D loops and an antisense nucleic acid sequence, which replaces stem-loop sequences removed from said U1 snRNA that are not in the C and D loops.

Izant teaches the chimeric antisense RNA molecules comprising an antisense sequence inserted into the 5' end of the U2 snRNA between the first and second loops (pp.187-190; Figure 2). Izant teaches that such chimeric RNAs are transported to the nucleus where they inhibited target gene expression (pp.188-9). Izant teaches that antisense sequences of longer than 260 nucleotides reduced accurate transcription of the chimeric constructs (p.188).

Zieve, et al. teach that U2 snRNAs have nuclear localization sequences at the 3' end of the molecule (p.26).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a U2 snRNA containing an antisense sequence for silencing target gene in a cell because Izant teaches such U2 snRNAs. It further would have been obvious to either make the chimeric constructs with antisense sequences less than 260 nucleotides in length or to replace part of the 5' end of the U2 snRNA sequence with a longer antisense sequence because Izant

teaches that longer chimeric transcripts were not accurately transcribed. One of skill in the art would recognize the need to maintain the secondary structure at the 3' end (C and D loops) of the antisense-snRNA chimeric molecules to ensure delivery of the molecules to the nucleus, because Izant indicates the chimeric molecules inhibit target gene expression in the nucleus and Zieve teaches that the 3' end secondary structure is necessary for nuclear import. Therefore, the instant claims would have been *prima facie* obvious to one of skill in the art at the time of the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK MCDONALD whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER PITRAK MCDONALD/
Primary Examiner, Art Unit 1635